REMARKS/ARGUMENTS

After entry of this amendment, claims 56-59 are pending in the present application. Previously pending claims 31, 32, and 37-55 are cancelled without prejudice. Applicants specifically reserve the right to pursue the cancelled claims in one or more subsequent applications. New claims 56-58 are directed to measuring binding between PI3 kinase and PDGF receptor *in vitro*. Support for new claims 57-61 can be found, for example, in the original claims, as well as throughout the specification. In particular, support can be found, for example on pages 59-61 and pages 83-84, which describe *in vitro* experiments designed to identify the site of interaction between PI3 kinase and PDGF receptor. Specifically, the specification teaches an *in vitro* assay on page 58 line 30 to page 59, line 6. These assays showed that phosphorylation of the Tyr residue at position 719 and/or 708 resulted in blocking of the interaction (*see* specification, page 61, lines 19-24 and page 63, lines 5-12).

The recited subsequences of the B type hPDGF-R find support in Table 1 and SEQ ID NO: 4. As explained at lines 3-6 of page 18, the numbering of residues in Table 1 is based on the mature protein, which ***excludes*** the first 32 amino acids of SEQ ID NO: 4. However, the numbering of residues in SEQ ID NO: 4 is based on the unprocessed protein, which ***includes*** the first 32 amino acids. Thus, corresponding residues in SEQ ID NO: 4 can be found by adding 32 to the residue numbers from Table 1. For example, the subsequence of SEQ ID NO: 4 corresponding to the kinase insert domain is described as extending from arg 663 to leu 766 of the sequence in Table 1. Residues 695 to 798 of SEQ ID NO: 4 corresponds to residues 663 to 766 of Table 1. Similarly, residues 604 to 951 of SEQ ID NO: 4 correspond to residues 572 to 919 of Table 1; residues 695 to 951 of SEQ ID NO: 4 correspond to residues 663 to 919 of Table 1; and residues 557 to 951 of SEQ ID NO: 4 correspond to residues 524 to 919 of Table 1. The phoshporylated tyrosine residues occur at positions 740 and 751 in SEQ ID NO: 4, which correspond to positions 708 and 719 in Table 1, respectively.

Withdrawn Claim Objections and Rejections

The Applicants gratefully acknowledge the Examiner's withdrawal of objections to claims 3, 16, 17 and 28 as well as the withdrawal of rejection of claim 31 under 35 U.S.C. §112, first paragraph and 35 U.S.C. §103, as indicated in the Office Action.

Claim Objections

Claims 42 and 43 are objected to because of informalities. These objections are rendered moot by cancellation of these claims. Withdrawal of the objections is respectfully requested.

Rejection Under 35 U.S.C. §112

The rejection of claim 31 as being allegedly indefinite for omitting essential steps, such as a correlation step, under 35 U.S.C. §112, second paragraph, is maintained. This rejection is also applied to claims 32 and 37-55.

The Examiner asserts that a correlation step defining a quantifiable relationship that is indicative of obtaining an effect is required in the claims. To advance prosecution, claim 56 specifies that the inhibitory effect of the test molecule is determined by comparing the amount of PDGF receptor binding to PI3 kinase in the presence of the test molecule to that in the absence of the test molecule. *In vitro* assays in which the binding between PDGF receptor and PI3 kinase is detected are described in detail, for example, on page 58 and 59 of the present application. Thus, the scope and meaning of the pending claims would be clear to one of skill in the art. Withdrawal of the rejection is respectfully requested.

Amended claims 31, 32 and 37-54 are rejected under 35 U.S.C. §112, first paragraph, as being allegedly not enabled.

On page 5, lines 1-5 of the Office Action, the Examiner acknowledges that the specification is enabled for a method of selecting molecules capable of inhibiting the binding between PDGF receptors and PI3 kinase by measuring binding between PDGF receptors and PI3 kinase or by measuring PI3 kinase activity. As noted above, to expedite prosecution, the claims

have been amended to specifically recite such methods. In light of these amendments, the Applicants respectfully request that the rejection be withdrawn.

Rejection Under 35 U.S.C. §103

Amended claims 31-32 and new claims 37-44 and 46-55 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Kazlauskas *et al.* (*Cell* (1989), 58:1121-1133) in view of Sporn *et al.* (*The Journal of Clinical Investigations* (1986), 78:329-332) and further in view of Matsui *et al.* (*Science* (1989), 243(4892):800-804) and Gronwald *et al.* (*Proc. Natl. Acad. Sci. USA* (1988), 85(10):3435-3439). The Office Action indicates that Kazlauskas *et al.* teach that autophosphorylation of PDGF receptors results in receptor activation and cellular changes, such as association of cellular polypeptides with the receptor and that the methods used by Kazlauskas *et al.* could be used as a method of screening compounds that inhibit the binding of two polypeptides, which is phosphorylation dependent, with at least one of the polypeptides being autophosphorylated PDGF receptors. Sporn *et al.* is cited for teaching that PDGF is involved in various types of cancers and that antagonists are viable options in fighting disease. Matsui *et al.* and Gronwald *et al.* are cited for teaching the sequence of PDGF receptor polypeptide sequences.

The pending claims are directed to use of subsequences of B type hPDGF-R comprising the kinase insert domain set forth in SEQ ID NO: 4. The present inventors have shown that PDGF-R and PI3 kinase directly interact and that the direct binding occurs in the kinase insert region around tyrosine 719, which is the same as tyrosine 751 of SEQ ID NO: 4. In particular, the present inventors used an *in vitro* system to directly study the interaction between the type B PDGF receptor and PI3 kinase (*see* specification states at page 58, lines 30-35). Starting at page 60, line 26, the specification describes a series of experiments designed to "identify the site of interaction between the receptor and the PI3 kinase." Based on these experiments, the present inventors concluded that direct binding between PDGF-R and PI3 kinase involves the kinase insert domain and that phosphorylation was required for the interaction (*See* page 64, lines 26-29). The present inventors also showed that there are two auto phosphorylation sites in this region, one at Tyr 740 and one at Tyr 751 (*see* specification, page

61, lines 19-24 and page 63, lines 5-12). As explained below, nothing in the cited references discloses or suggests that the kinase insert domain is the region of direct binding between these two proteins.

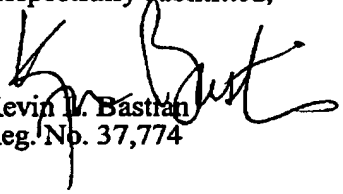
The primary reference, Kazlauskas *et al.*, teaches that phosphorylation of Tyr 751 is required for stable interactions between PDGF-R and other cellular proteins. The nature of the interaction or the region of the receptor that participates in the binding is ***not*** disclosed, however. Indeed, the authors describe their experiments as only establishing that "autophosphorylation of Tyr-751 provides the signal for a ***conformational change*** that allows stable interactions with a number of cellular proteins. (page 1130, left column, emphasis added). Thus, authors themselves suggested that phosphorylation leads to a conformational change that allowed binding and did not have a basis for predicting the exact nature of the interaction between the proteins. In addition, Kazlauskas *et al.* do not disclose or suggest the effects of phosphorylation at position 740 on binding.

The secondary references add nothing to the teachings of Kazlauskas *et al.* in this regard. As noted above, Sporn *et al.* is cited for teaching that PDGF is involved in various types of cancers and that antagonists are viable options in fighting disease. It provides no teaching with regard to the nature of the interaction between PDGF-R and PI3 kinase. Matsui *et al.* and Gronwald *et al.* are cited for teaching the sequence of PDGF receptor polypeptide sequences. Similarly, nothing in these references addresses the teaching missing from Kazlauskas *et al.* Thus, the cited references either alone or in combination fail to disclose or suggest the claimed methods. In light of the amendment and arguments presented above, the Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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